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Research has demonstrated that the majority of antihistamines (H1 antagonists) have sedative effects and can impair psychomotor performance; however, it is claimed that astemizole (hismanal) does not possess central nervous system side effects. A two-factor, repeated measures, double-blind design was used to compare the effects of three treatments (two antihistamines and one placebo) on cognitive information processing, mood, selected physiological measures, subjective feelings of drowsiness, and subjective performance ratings in 28 healthy men. Evaluations were given at 1,3,5,7,9,11,13, and 15 hours post ingestion.

Time-of-day effects were evident in following directions, unstable tracking, code substitution, serial addition/subtraction, logical reasoning, manikin, and pattern comparison tasks. A general trend of improved scores through the day was observed and a temporal pattern of a low performance was suggested in the afternoon (2:00 pm and 4:00 pm). Temporal effects were noted for physiological measures.

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SUMMARY

Benadryl produced performance decrements at one hour post ingestion on the following directions task, at one and a half hours on the unstable tracking task, and at three hours on the serial addition/subtraction task. No decrements in performance were found post ingestion of hismanal and, in fact, the hismanal group performed the serial addition/subtraction task more quickly than either the placebo or benadryl groups at five hours post ingestion. At three and a half hours post ingestion, the performance of the benadryl group remained poorer than the hismanal group on unstable tracking, but was not different from the placebo group.

A higher level of tension, greater fatigue, and lower level of activity was experienced post benadryl. Lower vigor-activity and higher confusion-bewilderment post hismanal and benadryl were noted one hour post ingestion; however, confusion was lower and activity was higher for hismanal than benadryl. Low vigor-activity, high confusion, increased sleepiness, and low perceived performance post benadryl persisted for three hours, while fatigue-inertia persisted for seven hours. Subjects were able to determine receipt of a placebo versus an antihistamine following ingestion of either a placebo or benadryl. Results suggest that hismanal is superior to benadryl for avoidance of subjective effects and performance of information processing tasks.

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

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N/A In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

X For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46.

N/A In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

H Snyder 4/13/90

PI Signature Date

This research was submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Department of Industrial Engineering and Operations Research, Human Factors Engineering Option, in the Graduate School of Virginia Polytechnic Institute and State University.

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INTRODUCTION

Individuals suffering from allergic rhinitis, perennial or seasonal (hay fever), with its associated symptoms (rhinorrhea-runny nose, pruritus-itching, and lacrimation-tearing) may be reluctant to seek medical attention for numerous reasons (for example, pilots may be reluctant to be taken off flight status and truck drivers or assembly line employees may resist being taken off of a job). Instead they may choose to self medicate with available over-the-counter medications. These drugs, many of which are antihistamines (such as benadryl) or contain antihistamines (cold medications) can cause sedation and result in performance deficits. For pilots, Whitehurst (1980) cautions against the use of drugs which may potentially affect pilot judgement, vision, or fine motor coordination, or which may reduce tolerance to hypoxia. Antihistamines are included in this list. Identification of a medication that does not cause sedation would allow physicians to prescribe medications which would permit missions to proceed unhampered by either the symptoms of the illness or the side effects of the drug.

In addition, an assessment battery that is sensitive to therapeutic doses of antihistamines could be used as an assessment tool to determine an individual's ability to perform certain activities (given that the activities require skills which are similar to those tested in the assessment battery). The assessments may also be applicable to other drugs, such as other antihistamines, drugs essential during chemical warfare (antidotes), or drugs used to treat other medical conditions. The methods of evaluation currently used in antihistamine/psychomotor research and the evaluations themselves are not comparable across studies. The exact manner in which the tasks are developed, administered, and scored are often not reported in the literature or differ from one study to another. For example, Fink and Irwin (1979) did not pre-train subjects, Moskowitz and Burns (1988) gave two training sessions, while Unchern, Unchern, Chumsawat, Sriwatanakul, and Limsuwan (1986) trained subjects for one full day so that they reached "optimal performance level." In addition, there are many types of tracking tasks and many forms of digit symbol substitution and arithmetic tasks. The standardization of performance evaluations and the methodology used is of utmost importance for comparison of research findings.

Assessments used in this research included portions of the Unified Tri-Service Assessment Battery (UTC-PAB) and the Complex Cognitive Assessment Battery

(CCAB). These computerized assessment batteries were developed for use in assessment of the effects of pre-treatment drugs (medications which are used as counter agents in chemical warfare) on the complex cognitive abilities required to perform critical U. S. Army tasks (Analytical Assessments Corporation, 1988; Perez, Masline, Ramsey, and Urban, 1987).

RESEARCH OBJECTIVES

The objectives of this research were (1) to determine whether selected cognitive tasks show performance deterioration under the influence of two antihistamines (benadryl and hismanal) and (2) to determine the subjective effect of the antihistamines and whether research subjects could detect their own performance decay.

Based on the literature review, central nervous system effects such as sedation, drowsiness, and altered psychomotor performance are expected following ingestion of benadryl (Nicholson, Smith and Spencer, 1982; White and Rumbold, 1988). Previous research (with therapeutic doses of benadryl) has yielded conflicting results on arithmetic (simple addition/subtraction) and reaction time tasks. Visual-motor tracking, digit-symbol substitution, visual search, vigilance, and divided attention tasks have yielded significant effects, that is, performance decrements. In accordance with the literature, it was expected that decrements would be evident during test sessions one (one hour post ingestion) and two (three hours post ingestion) on the unstable tracking, code substitution, and divided attention (Following Directions) task with benadryl. No significant effects were expected following hismanal ingestion on any of the subtasks and performance was not expected to differ from performance following ingestion of a placebo.

It was expected that subjective reports of mood would differ following ingestion of benadryl, again during the first and second test sessions (one and three hours post ingestion) and that symptoms such as sleepiness, drowsiness, mental and physical sedation, fatigue, and lowered ability to concentrate would be identified (Carruthers, Shoeman, Hignite, and Azarnoff, 1978; Cohen, Hamilton and Peck, 1987; Jaattela, Mannisto, Paatero, and Tuomisto, 1971; Moskowitz and Burns, 1988). Moskowitz and Burns (1988) did not find significant differences in subjective reports five hours post ingestion of benadryl. As no research was identified in the literature review which continued for the time length (16 hours) to be used in this study, it was unknown whether subjective reports would differ beyond five hours post ingestion. A fatigue effect was

expected post benadryl ingestion in comparisons with placebo ingestion. No significant differences in subjective reports were anticipated following hismanal ingestion (Krstenansky and Cluxton, 1987; Wihl, Petersen, Perterson, Gundersen, Bresson, and Mygind, 1985; Vanden Bussche, Rombaut, Schuermans, Gijpen, Dom, and Moens, 1984). Subjective ratings of mood following hismanal ingestion were not expected to differ from ratings following ingestion of a placebo.

Research has indicated that subjects are able to identify their own performance decay during a driving task (Betts, Markham, Denenham, Mortiboy, and McKevitt, 1984) as well as during psycho-motor performance tasks (Moskowitz and Burns, 1988). It was expected that subjects' ratings of their performance would accurately reflect their performance deterioration.

RESEARCH DESIGN

Analysis of variance (ANOVA) procedures were performed on dependent variables for each task. Post-hoc simple-effect F-tests were performed to evaluate significant interactions. The Newman-Keuls test was performed to compare means. For all ANOVA procedures and the Newman-Keuls tests an alpha level of 0.05 was adopted. The Statistical Analysis System (SAS, version 5.18) was used for all analyses with the exception of the simple-effect F-tests.

To determine the subjective effect of antihistamines an ANOVA was performed on the two mood scales, Mood Scale II from the Uniformed Tri-service Performance Assessment Battery and the Profile of Mood States, on the Stanford Sleepiness Scale, and on the self rating of perceived performance. To assess the ability of subjects to detect their own performance decay, the Spearman Rank Correlation was performed which examined subjects' self rating of their performance to their actual scores for accuracy and speed on the Uniformed Tri-service Performance Assessment Battery subtests.

The basic experimental design was a Latin square (drug x order x time), which was used to counterbalance order of presentation. To assess the drug effect, independent of the order of drug presentation, it was desirable to collapse the data across order, assuming order to be nonsignificant. Therefore, in order to determine if the order of drug administration had an effect, an analysis of variance procedure was used on the dependent variables mean reaction time and number of errors for the Uniformed Tri-service Performance Assessment Battery tasks, the root-mean-square error for the unstable

tracking task, and score for the Complex Cognitive Assessment Battery tasks. There were six orders of the three drug conditions. The following equation was applied:

$$P_I = 1 - (1 - \alpha)^N,$$
$$.01 = 1 - (1- \alpha)^{16},$$
$$\alpha = .0006279,$$

where

P_I = the experimentwise probability of a Type I error existing among all comparisons, set at 0.01,

α = the significance level used per comparison, and

N = the number of dependent-variable comparisons made, which was 16.

Using this analysis, one order effect was significant, no pattern or trend was evident, and no interactive effects of drug x order were found. Therefore, the order variable was disregarded in all subsequent analyses (resulting in a 3 x 8 experimental design).

RESULTS

Complex Cognitive Assessment Battery

Two subtests from the Complex Cognitive Assessment Battery (CCAB) were used. They were the Following Directions task and the Route Planning task. The Following Directions task was subject to temporal effects which may be indicative of learning throughout the day. This result, in turn, could suggest that the level of training was insufficient. Although the benadryl group's performance was lower than the other groups during the 8:00 am session, the sole dependent measure which ascertained the effect of benadryl was the percent total hits on the hard level task. There also appears to be a circadian effect in which performance decreases during the 2:00 pm and 4:00 pm sessions, which is indicated most frequently in the easy level task. The lowest performance was typically observed during the first session and the highest performance was seen during the last sessions of the day.

The software for the Route Planning task is not programmed appropriately. Solutions which are correct can be achieved in fewer moves than the program recognizes. This should not affect the score, however, as score is equal to accuracy * speed * problem difficulty * range constant. None of the dependent measures was found to be of sufficient

sensitivity to detect the effects of the antihistamines used. Temporal fluctuations suggest that subjects performed best at noon and in the early evening and worst at 8:00 am, 10:00 am, 4:00 pm, and 10:00 pm. A collective improvement of scores over time was not observed for this task. Both tasks generally showed low performance during the early sessions, in the late afternoon, and during the last session of the day.

Unified Tri-Service Assessment Battery

Nine tasks were used from the Unified Tri-Services Performance Assessment Battery (UTC-PAB) (Hegge, Reeves, Poole, and Thorne, 1985). Eight of the tasks were written at the Walter Reed Army Institute of Research and are part of the Walter Reed Performance Assessment Battery (Thorne, Genser, Sing, and Hegge, 1985). The Unstable Tracking task was written by Systems Research Laboratory (1987).

Temporal effects were noted for eight of the nine tasks. Although subjects trained for one and a half hours to two hours on the UTC-PAB tasks and one hour on the tracking task, an apparent learning effect was evident in all cases (except for Time Wall and Interval Production). A performance decrement was suggested in the afternoon on six of the tasks, which may implicate a circadian pattern of a low performance period occurring in the afternoon. For the Time Wall task it was found that judged time decreased over the course of the day, which is opposite to that found by Jerison and Arginteanu (1958, as cited by Perez et al., 1987), who found that subjects increased their time estimation over repeated trials.

Performance decrements due to the antihistamine ingested were found on the Serial Addition/Subtraction task and the tracking task. Mean reaction time was slower at 10:00 am post benadryl ingestion as compared to hismanal or placebo on the Serial Addition/Subtraction task. Mean reaction time at 12:00 pm was faster post hismanal ingestion than for the other two conditions on the same task. Subjects were less able to maintain center control of the cursor on the Unstable Tracking task post ingestion of benadryl at 8:00 am than for the other two conditions. At 10:00 am, performance following benadryl ingestion remained poorer than following hismanal ingestion, but was not different from the placebo.

In order to evaluate further each of the tasks, performance scores were correlated with self reports of levels of experience with video games, computer programming, word processing, hours spent using a computer per week, chess experience, and number of post

high school math classes. Word processing experience was not found to be related to any of the task scores. Although a relationship was found between hours spent using a computer per week and errors on logical reasoning and serial addition/subtraction tasks, no interpretation was possible due to poor definition of the work done when using the computer. A correlation was found between experience with the game of chess and reaction time on the code substitution task, in which large chunks of information had to be memorized, and scores on the route planning task, which used the knight's move from chess. The number of post high school math classes taken was found to be correlated with the serial addition/subtraction task. A relationship was found between experience with video games and reaction times on the four choice reaction time task and scores on the route planning task . Finally, computer processing experience was found to be correlated with reaction time on the code substitution, logical reasoning, and serial addition/subtraction tasks and with accuracy scores on unstable tracking, following directions, and route planning tasks. This information does not intimate that performance scores on identified tasks were the result of high levels of experience in the associated areas. Although correlations were significant, they were not great in magnitude (all less than 0.60). These results signal the need for further research as underlying skills for associated experience and tasks may be similar. Research with individuals who have high levels of experience in an area such as computer programming may tend to influence research results. For example, if the level of chess experience is associated with performance scores on the route planning task, this association may interfere with the effects of the independent variable under investigation.

Physiological Measures

Temporal effects were noted for systolic blood pressure, pulse, and temperature. Systolic blood pressure was lowest during the morning sessions and noon session and highest at 2:00 pm and 10:00 pm. The fastest pulse rate was obtained at 2:00 pm while the slowest pulse rate was obtained at 12:00 pm. Temperature was lowest in the morning and increased throughout the day.

Mood Scales

Temporal effects were found for the activity subscale of Mood Scale II and the vigor-activity subscale of the Profile of Mood States (POMS). The level of vigor was lowest during the first two sessions and increased throughout the day. As previously stated, one plausible explanation for the increased activity level over the course of the day is the activity level of students may be greatest during the evening (study or social) hours.

Drug effects were seen on the tension-anxiety, vigor-activity, and fatigue-inertia subscales for POMS. The overall trend was that a higher levels of tension-anxiety and fatigue-inertia and a lower level of vigor-activity was experienced by the benadryl group. As noted by Gengo et al. (1989), subjective reports of fatigue following benadryl ingestion lasted for up to six hours.

Time x drug interaction effects were noted for the activity, depression, anger, and fatigue subscales on Mood Scale II. Interaction effects were also found for the vigor-activity, fatigue-inertia, and confusion-bewilderment subscales of POMS. On both Mood Scale II and the POMS, the placebo group reported a higher level of vigor than did either the hismanal or benadryl groups during the 8:00 am session. Additionally, the hismanal group reported a higher level of vigor than did the benadryl group on the POMS. During the 10:00 am session, both the placebo group and the hismanal group reported a higher level of vigor than did the benadryl group on both mood scales. The difference between the placebo and benadryl groups was expected and supports previous research results (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). The difference between the placebo and hismanal groups was not expected as hismanal is reported to be void of central nervous system effects such as drowsiness (Chapman and Rawlins, 1982; Nicholson, Smith, and Spencer, 1982; Nicholson and Stone, 1982; Richards, Brogden, Heel, Speight, and Avery, 1984) and research has indicated that subjective reports do not differ from placebo (Nicholson et al., 1982; Nicholson and Stone, 1982).

For both the fatigue subscale from Mood Scale II and the fatigue-inertia subscale on the POMS, the benadryl group reported higher levels of fatigue than did either the placebo or hismanal groups for the first two sessions of the day. At 12:00 pm and 2:00 pm, the benadryl group reported higher levels of fatigue than did the placebo group for both subscales. These results support findings of sleepiness, drowsiness, mental and physical sedation, fatigue, and decreased concentration following ingestion of benadryl

(Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). These findings also agree with research that found that subjective reports post hismanal ingestion do not differ from placebo (Nicholson, Smith, and Spencer, 1982; Nicholson and Stone, 1982).

A higher level of confusion was reported by the benadryl group than by both the placebo and hismanal groups during the 8:00 am session. Also at 8:00 am, the hismanal group reported a higher level of confusion than did the placebo group. A higher level of confusion was reported by the benadryl group than both the placebo or hismanal groups at 10:00 am. The adjectives used for the confusion subscale relate to feelings of unclear thinking and disorganization. Previous research has noted increased mental sedation and decreased concentration post ingestion of benadryl which would support these findings (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). The difference between the hismanal and placebo group is more difficult to explain as hismanal is reported to be devoid of central nervous system side effects such as sedation and fatigue.

Self Ratings

Three forms of self rating were used. They included: (1) the Stanford Sleepiness Scale, which is included in the Walter Reed Performance Assessment Battery (Thorne et al., 1985), (2) a self assessment of whether subjects believed they had received an antihistamine or a placebo, and (3) a self evaluation of how subjects felt they had performed (on the UTC-PAB tasks) during each session. The Stanford Sleepiness Scale and perceived performance ratings were composed of Likert-scale response data. The self assessment of medication is composed of nominal data.

Self reports of sleepiness, using the Stanford Sleepiness Scale, revealed that the level of sleepiness varied both by time of day and the time of day x drug interaction. The level of reported sleepiness decreased throughout the day, with a suggestion of a dip at 12:00 pm. The highest levels of sleepiness were reported at 8:00 am and 10:00 am, while the lowest levels were reported at 10:00 pm, 8:00 pm, 6:00 pm, and noon. The increase in sleepiness during the afternoon reflects the decreased performance trends seen in unstable tracking, code substitution, logical reasoning, pattern recognition, manikin, and serial addition/subtraction, and may be indicative of circadian patterns and/or sleepiness

following ingestion of lunch. The temporal decrease in sleepiness is inversely related to the profile of mood state subscale for vigor-activity.

A closer look at the interaction effect reveals that reported sleepiness was higher post benadryl than post placebo or hismanal at 8:00 am and 10:00 am . It is interesting to note that the level of increased sleepiness was significant for only the first two sessions on the Stanford Sleepiness Scale, while high levels of fatigue were reported through the 2:00 pm session for both Mood Scale II and the Profile of Mood States.

There was a difference in rating according to which drug/medication the subject received. Results were analyzed using the Sutcliffe (1957) Chi-square analysis, which allows frequency data to be analyzed for interactions as well as main effects. All responses were evaluated to view how they were distributed according to personal responses; therefore, there is no drug effect evident. The results reveal that there was an effect for self rating and that the self rating was different for different drugs. To further examine the interaction, ratings were assessed separately for each drug using a 1-way Chi-square for each. Significant differences were seen for the placebo and benadryl groups. Subjects responded that they had received a placebo more often when actually receiving a placebo and as having received an antihistamine after receiving benadryl. No difference was found for the hismanal group.

The frequency of reported symptoms for each drug was analyzed using the Sutcliffe (1957) chi-square analysis. The results were analyzed for number of symptoms x drug x time. There were three symptom categories which were (1) no symptoms, (2) 1 to three symptoms, and (3) four or more symptoms. All responses were evaluated; therefore, there is no main effect of drug, symptoms, or time that is possible. The results reveal that there was an effect for the drug x symptom interaction.

In order to further examine this effect, 1 x 3 Chi-square tests were performed on each of the symptom categories. A significant difference was seen only for the third symptom category (four or more). Subjects that received benadryl reported a much higher number of symptoms in the third category, while the placebo group reported a much lower number of symptoms. This effect is also reflected in the total number of symptoms per drug. These results support literature which cites antihistamines as producing side effects such as loss of appetite, nausea, vomiting, epigastric distress, constipation, diarrhea, dryness of mouth, frequent urination, hypertension or hypotension, headache, faintness, tightness of the chest, and visual disturbances (Bergersen, 1979; Di Palma, 1971).

An ANOVA was performed on the five categories of perceived performance. Findings were significant for time of day, drug, and the time x drug interaction. Subjects rated their performance lowest at 10:00 am and highest at 10:00 pm. Perceived performance was higher post placebo than post benadryl. The drug effect was significant during the 8:00 am and 10:00 am sessions. Subjects perceived their performance as higher post placebo or hismanal as compared with benadryl during the two morning sessions.

These findings are more applicable to work settings if perceived performance is indicative of actual performance. The Pearson product-moment correlation was used to compare the scores achieved on UTC-PAB performance tests with the five categories of perceived performance. Results suggest that subjects were somewhat able to evaluate their own performance on more complex tasks as indicated by both errors and mean reaction time scores, although the correlations are quite low. Subjects were not able to significantly assess their performance on four-choice reaction time, time estimation, and interval production tasks.

Learning Effect

In order to further examine the question of whether the improvement seen on several of the performance tests during the day were indeed due to a learning effect and to discover whether this effect continued over days, a comparison was made across the three test days for the placebo condition only. The dependent variable mean reaction time was used for the Pattern Recognition, Logical Reasoning, Manikin, Serial Addition/Subtraction, and Time Wall tasks. Both errors and mean reaction time were used for the Code Substitution task. Root-mean-square error and boundary hits were used for the Unstable Tracking task. On the Following Directions task, total time, percent total hits, and mean time were used for the easy difficulty level. Mean time was used for the medium difficulty level. Score, total time, percent total hits, and mean time were used for the hard level. On the Route Planning task, number of reversals were used for the hard difficulty level. These dependent variables were noted to improve over time in the original analysis.

There was a difference across the three days for the Manikin task, boundary hits and root-mean-square error on the Unstable Tracking Task, and percent total hits for both the easy and hard difficulty levels on the Following Directions Task. In the Manikin Task,

the mean time for Day 1 was much slower than for the following two days. On the Unstable Tracking task, there were fewer boundary hits on Day 3 as compared with Day 1 and the root-mean-square error was lower on Day 3, compared with Day 2. On the Following Directions Task - both easy and hard levels, the percent total hits was higher on day 3 as compared with Day 1. Improvement over the three test days was seen on the Following Directions percent total hits - easy and hard levels, boundary hits and root-mean-square error on Unstable Tracking, and mean reaction time on the Manikin task. Performance appears to continue with practice on these three tasks.

The temporal effects seen on the overall analysis were not present with the same level of consistency for the placebo data only. Time effects within days were seen on only 5 of the 19 dependent variables. The significant dependent variables are Serial Addition/Subtraction mean reaction time, Unstable Tracking boundary hits, and three Following Directions variables. As seen graphically, the mean reaction time generally decreased throughout the day. The longest mean reaction time occurred at 12:00 pm and the shortest mean reaction time occurred at 10:00 pm and the absolute differences were small. Although the number of boundary hits on the Unstable Tracking Task was found to vary by time of day, there was no difference in the means as indicated by the Newman-Keuls test and less than one boundary hit occurred at each time of day. The Following Directions significant dependent variables are score - hard level task, total time - hard level task, and mean time - medium level task. The score - hard level task generally improved throughout the day, with the two lowest scores occurring at 8:00 am and 10:00 am and the highest score at 10:00 pm. The total time - hard difficulty level decreased over the day with the longest times occurring during the two morning sessions and the shortest time at 10:00 pm. The mean time - medium level was slowest at 4:00 pm and fastest at 8:00 pm and 10:00 pm. These results indicate that improvement within days transpired on only two dependent variables, Following Directions score - hard difficulty level and Following Directions total time - hard difficulty level.

The difference between the time of day results on the overall analysis and the placebo data appears to be the result of the drug effect having amplified the time of day effect when using the three treatment days in the analysis.

CONCLUSIONS

Complex Cognitive Assessment Battery

Time of day effects were noted on the Following Directions easy and hard level tasks. Performance was observed to be lowest during the morning sessions and to improve throughout the day, with suggested performance decrements during the 2:00 pm and 4:00 pm sessions indicated most frequently in the easy level task. This trend suggests a circadian pattern. No significant effects were noted for dependent variables on the medium level task with the exception of mean time. Although performance following ingestion of benadryl was lower than for hismanal or placebo during the 8:00 am session on several measures of both the easy and hard level tasks, the sole dependent measure which ascertained the effect of benadryl was the percent total hits on the hard level task. At 8:00 am, the benadryl group achieved fewer total hits than did either the hismanal or placebo groups. Although, no similar tasks were noted in antihistamine research literature, this task requires divided attention similar to that of a combined memory search and tracking task.

The Following Directions task requires memory storage and memory retrieval simultaneous with visual search and manual task execution, thus necessitating time sharing of cognitive, perceptual, and motor response skills (Analytical Assessments Corporation/EATON Corporation, 1988). The results of this research support findings by Moskowitz and Burns (1988) in which tracking, divided attention, and vigilance were significantly affected at one hour post ingestion of 50 mg of benadryl. However, Moskowitz and Burns (1988) also found performance decrements at three hours post ingestion on visual search, tracking, and divided attention. Gengo et al. (1989) found that performance decrements on a driving simulator and digit symbol substitution task lasted for only two hours.

The research results from this battery indicate the following conclusions.

(1) Further research is desired with an increased diversity of subjects to eliminate the possible arousal effect of a student population, which may typically be more alert in the afternoon and evening hours.

(2) The easy level Following Directions task does not appear sensitive to the antihistamines used in this research at therapeutic dose level effects. More research should

be conducted to determine the sensitivity of this task to other medications and other dose levels.

(3) The medium level task does not appear to be a reliable performance indicator as the dependent measures were insensitive to both time and drug effects. It is not recommended for further use in performance or drug testing until an evaluation of its sensitivity has been completed.

(4) The hard level task demonstrated the clearest temporal effect and the only performance decrement (8:00 am) due to antihistamine ingestion. This task possesses the greatest promise for future use in medication evaluations. More research is needed to assess possible learning effects.

(5) A pattern of decreased performance was suggested during afternoon sessions (2:00 pm and 4:00 pm). In order to interpret these results, future research should attempt to control for sleep levels, diet, and activity between test sessions.

In Route Planning, score on the hard level task and number of reversals on both the hard and easy levels were found to vary with time. However, there was no difference in the means on the Newman-Keuls test for score and easy level reversals. Temporal effects for the hard level task suggest that subjects performed best at 6:00 pm and worst at 4:00 pm and 10:00 pm, which is a pattern not seen for other tasks.

As correct solutions can be achieved in fewer moves than the program for the Route Planning task recognizes (or corrects for), values for the variable minimum valid moves cannot be interpreted and therefore should not be utilized as a dependent measure until the software is corrected. None of the dependent measures was found to be of sufficient sensitivity to detect the effects of the antihistamines used. A solution was achieved only 86.81 % of the time. The inability to achieve a correct solution occurred regardless of the drug condition. The difficulty in achieving the correct solution may have contributed to the lack of main and interactive effects observed. In addition, noting that correct solutions can be achieved in fewer moves than the software program recognizes does not encourage confidence in the software program or the recording of whether a correct solution was achieved. As this task required the use of the knight's move in the game of chess, it is interesting to note that subjects' self ratings of their ability levels at chess was correlated significantly with their scores ($\rho = 0.4004, p = 0.0347$). Further training could possibly alleviate this influence; however, it is important to keep this issue in mind when using a portion of a learned skill (such as chess) to evaluate the effects of an independent variable such as medication. Experts may be better able to override the effects

of the medication. If the results obtained from this task are reliable, then the following conclusions are warranted.

(1) Neither the easy nor the hard level Route Planning tasks appear sensitive to the antihistamines used in this research at therapeutic dose levels. More research should be conducted to determine the sensitivity of this task to other medications and other dose levels.

(2) The medium level task does not appear to be a reliable performance indicator as it was insensitive to both time and drug effects. It is not recommended for further use in performance or drug testing until an evaluation of its effectiveness has been completed.

(3) In order to interpret temporal effects, future research should attempt to control for sleep levels, diet, and activity between test sessions.

(4) Further research should address the issue of personal background and experience levels at related tasks (such as chess). Until completion of such research, caution on interpretation of results is advised.

In view of the low frequency of solutions achieved, the software problems in recognition of correct solutions, and the lack of sensitivity to the effects of the antihistamine levels used in this study, this task is not recommended for evaluation of pharmaceuticals. It is recommended that the software for this task be examined and corrected as necessary. Consequent to this, the task may be re-evaluated for usefulness in performance and pharmaceutical research.

Unified Tri-Service Assessment Battery

Temporal effects were evident in Unstable Tracking, Code Substitution, Serial Addition/Subtraction, Logical Reasoning, Manikin, and Pattern Comparison tasks. Mean reaction time decreased without a decrease in accuracy, which suggests that the level of training may have been insufficient. A suggestion of low performance was observed in the early afternoon (2:00 pm and 4:00 pm), which may be the result of diurnal rhythms or post-prandial effects. Post-prandial effects have been noted to decrease performance (Christie and McBrearty, 1979; Taylor and Rachman, 1988, as cited by Mindell, 1990; Wurtman, 1986). For the Time Wall task it was found that judged time decreased over the course of the day, which is opposite to that found by Jerison and Arginteanu (1958, as cited by Perez et al., 1987), who found that subjects increased their time estimation over

repeated trials. The time of day effects do not appear to be the result of overall learning, as subjects did not continue to improve over consequent days.

Performance decrements due to the antihistamine ingested were found on the Serial Addition/Subtraction task and the Unstable Tracking task. Mean reaction time was slower at 10:00 am for the benadryl group than for the other two groups on the Serial Addition/Subtraction task. Performance at 12:00 pm was quicker for the hismanal group than for the other two groups on the same task. Previous research with therapeutic doses of benadryl yielded conflicting results on arithmetic tasks. The tasks utilized in other research involved simple addition and subtraction and therefore appear to differ from the serial addition/subtraction task used in this study. The task used in this research was machine- rather than self-paced, required sustained attention, and required a secondary process of either entering the least significant digit if the answer was positive or adding 10 to the answer if it was negative. On the tracking task, subjects were less able to maintain center control of the cursor post ingestion of benadryl at 8:00 am than for the other two groups. As the tracking task was one of the two last tasks in the battery, actual performance of the task (for the 8:00 am session) occurred at one and a half hours post ingestion of benadryl (8:30). At 10:00 am, the performance of the benadryl group remained poorer than the hismanal group, but was not different from the placebo group. These results lend support to findings of tracking effects found at one and a half (Moskowitz and Burns, 1988) and two hours (Cohen, Posner, Ashby, Smith, and Peck, 1984) post ingestion of benadryl (50 mg).

The research results suggest the following conclusions.

(1) Further research with a greater subject diversity is needed to investigate the time of day effects as students may be more alert in the afternoon and evening hours.

(2) Future research to accurately interpret temporal effects for possible post-prandial effects is necessary. Research should control for activity and diet during testing. Research should also control for sleep prior to data collection.

(3) Performance decrements due to antihistamine ingestion were noted at 10:00 am on the serial addition/subtraction task mean reaction time and at 8:00 am for the root-mean-square error for unstable tracking. These two tasks appear to have potential in evaluation of performance effects secondary to antihistamine use.

Experience Ratings

The correlations indicate the need for caution in application of skill-based performance evaluations. Individual differences based on past experience or skill levels on similar tasks could influence research results. Further research is necessary to determine whether such influence interferes with the effects of the independent variables, such as medications.

Summary of Performance Data

Temporal effects were evident in Following Directions, Unstable Tracking, Code Substitution, Serial Addition/Subtraction, Logical Reasoning, Manikin, and Pattern Comparison tasks. These results suggests that subjects' performance improved over the day, possibly due to circadian patterns. A pattern of a low performance was suggested in the afternoon (2:00 pm and 4:00 pm), which may be the result of diurnal rhythms or post-prandial effects.

Performance deterioration was expected post ingestion of benadryl on the subtasks which were considered to be of higher complexity and to place higher cognitive demands on subjects at one and three hours post ingestion of benadryl. Decrements in performance were therefore expected on the Route Planning and Following Directions tasks. In accordance with the literature review, performance changes were also anticipated on unstable tracking and code substitution tasks. The logical reasoning task was not noted in the literature as being used in antihistamine research; however, as it was expected to tap higher cognitive functioning it was also expected to yield to the negative effects of benadryl. The UTC-PAB version of the serial addition/subtraction task demanded a higher level of information processing than did addition/subtraction tasks described in other antihistamine research; therefore, this task was also expected to display performance deficits due to benadryl ingestion. No change in performance was anticipated with either the hismanal or placebo groups.

Decreased performance was found at one hour post ingestion of benadryl (50 mg) on the Following Directions task, at one and a half hours post ingestion on the Unstable Tracking task, and at three hours post ingestion on the Serial Addition/Subtraction task. Gengo et al. (1989) found performance effects lasted only two hours post ingestion on driving simulation and digit symbol substitution tasks. These results for the Serial

Addition/Subtraction task extend that time limit. In addition, results suggest that the type of skill affected by ingestion of benadryl may vary by time post ingestion. No decrements in performance were found post ingestion of hismanal and, in fact, the hismanal group performed the serial addition/subtraction task quicker than either the placebo or benadryl groups at five hours post ingestion. At three and a half hours post ingestion, the performance of the benadryl group remained poorer than the hismanal group on unstable tracking, but was not different from the placebo group. Performance impairment was not observed on tasks thought to emphasize perceptual input, detection, and identification (four-choice reaction time), central processing (code substitution), linguistic information integration and manipulation (logical reasoning), spatial information integration/manipulation (time wall, manikin, and pattern comparison), or output without a sustained visual component (interval production). As low doses used in this study impaired the three tasks which required sustained attention and the two tasks which required the highest levels of manual task execution in this battery, cognitive impairment of these drugs may be missed if tasks which do not require similar skills are not used. Moskowitz (1984) asserts that tasks requiring concentrated attention and divided attention are differentially affected by various drugs and that both performance dimensions must be included in medication evaluations.

Physiological Tests

Temporal effects were noted for systolic blood pressure, pulse, and temperature. These changes may be the result of either circadian patterns or meal ingestion. Pulse rate was found to be quickest after meals (2:00 pm and 8:00 pm) and slowest prior to meals (12:00 pm and 6:00 pm). Recorded temperature was lowest in the morning and increased throughout the day. No main effects of drug were noted for physiological measurements. These results support findings by Craft et al. (1987) in which no changes were observed in heart rate or blood pressure post ingestion of hismanal.

Mood Scales

Temporal effects were found for the activity subscales for both Mood Scale II and Profile of Mood States (POMS). Reported activity level was lowest during the two morning sessions and increased throughout the course of the day, although no difference

in means was found for Mood Scale II. A significant time of day effect was also noted for mean reaction time on Mood Scale II; as the day progressed, mean reaction time decreased. These results reflect the temporal effects found on performance tasks. As noted previously, one plausible explanation for the increased activity level over the course of the day is that university students may be more active during evening hours. The suggested afternoon effects could also be due to post-prandial effects. Christie and McBrearty (1979) assessed mood using the Nowlis Mood Adjective Check List a half hour before lunch and one and a half hours and three hours post lunch. They found that activity decreased and deactivation increased in the session immediately following lunch and returned to post lunch levels during the final session. They regarded these results as a reflection of a "post prandial lassitude" in the 1-2 hours post lunch period (Richards, 1971, as cited by Christie and McBrearty, 1979).

Drug effects were seen on the tension-anxiety, vigor-activity, and fatigue-inertia subscales for POMS. The overall effect was that a higher level of tension-anxiety and a lower level of vigor-activity was experienced by the benadryl group throughout the day. On the fatigue-inertia subscale, the benadryl group reported a higher level of fatigue primarily during the two morning sessions. These results support findings in which symptoms of sleepiness, drowsiness, mental and physical sedation, fatigue, and lowered ability to concentrate post benadryl ingestion have been reported (Carruthers et al., 1978; Cohen, Hamilton, and Peck, 1987; Jaattela et al., 1988; Moskowitz and Burns, 1988) and refute the finding of no mood effect found by Miller et al. (1988).

Time x drug interaction effects were noted for the activity, depression, anger, and fatigue subscales on Mood Scale II, as well as a marginally significant finding for mean reaction time ($F = 1.72, p = 0.0507$). Interaction effects were also found for the vigor-activity, fatigue-inertia, and confusion-bewilderment subscales of POMS. The placebo group reported a higher level of activity than did either the hismanal or benadryl groups during the 8:00 am session on both mood scales, while the hismanal group reported a higher level of activity than did the benadryl group on the POMS. At 10:00 am, both the placebo and the hismanal groups reported a higher level of activity than did the benadryl group on both mood scales. The difference between the placebo and benadryl groups was expected and supports previous research results (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). The difference between the placebo and hismanal groups was not expected as hismanal is reported to be void of central nervous system effects such as drowsiness (Chapman and Rawlins, 1982;

Nicholson et al., 1982; Nicholson and Stone, 1982; Richards et al., 1984) and research has indicated that subjective reports do not differ from placebo (Nicholson et al., 1972; Nicholson and Stone, 1982).

For both mood scales, higher levels of fatigue were reported for the benadryl group than for either the placebo or hismanal groups for the first two sessions. At 12:00 pm and 2:00 pm, the benadryl group reported higher levels of fatigue than did the placebo group for both subscales. These results support findings of sleepiness, drowsiness, mental and physical sedation, fatigue, and decreased concentration following ingestion of benadryl (Carruthers et al., 1978; Cohen et al.. 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). These findings also agree with research that found that subjective reports post hismanal ingestion do not differ from placebo (Nicholson et al., 1982; Nicholson and Stone, 1982). This is an hour longer than subjective reports of fatigue following benadryl ingestion as reported by Gengo et al. (1989).

A higher level of confusion (POMS) was reported by the benadryl group compared with both the placebo and hismanal groups during the 8:00 am session and greater confusion was reported for the hismanal group compared with the placebo. A higher level of confusion was reported by the benadryl group than both the placebo or hismanal groups at 10:00 am. As previously stated, the adjectives used for the confusion subscale relate to feelings of unclear thinking and disorganization. Previous research has noted increased mental sedation and decreased concentration post ingestion of benadryl which would support these findings (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988).

Although the anger and depression subscales on Mood Scale II were found significant for the interaction of time x drug, none of the individual sessions reached a level of significance. The benadryl group did report higher levels of anger and depression during the first two sessions of the day, but inexplicably the placebo group was also noted to report high levels of anger and depression during the final sessions of the day. There was no interactive effect for the subscale anger-hostility on the POMS. These findings lead one to conclude that the anger subscale may not be of sufficient sensitivity to reliably register antihistamine effects in this study.

The research results suggest the following conclusions.

(1) Further research with populations other than university students is necessary to evaluate temporal effects on subjective vigor-activity levels. Research should control for sleep levels prior to testing. Diet and activity should be controlled on test days.

(2) Both Mood Scale II and the POMS are of sufficient sensitivity to register variation in mood post antihistamine ingestion. This sensitivity was evident in the overall drug effect (tension-anxiety, vigor-activity, and fatigue-inertia scales on the POMS) and the drug x time interactions (activity and fatigue scales on Mood Scale II and vigor-activity, fatigue-inertia, and confusion-bewilderment scales on the POMS).

(3) The POMS appears to have greater sensitivity to the effects of the antihistamines than does Mood Scale II. Further research is needed with an increased number of subjects using both the abbreviated mood scale (Mood Scale II) and the longer version (Thorne et al., 1985). Prior to the conclusion of the suggested research, the POMS is recommended for antihistamine research.

(4) Subjective differences due to antihistamine ingestion (benadryl) were found for three hours post ingestion for vigor-activity and confusion-bewilderment scales and seven hours for the fatigue and fatigue-inertia scales. Post benadryl ingestion, the subjective feeling of fatigue persists beyond the time when performance effects are evident.

(5) Activity was reduced and confusion-bewilderment was increased at one hour post ingestion for hismanal as compared with placebo. These unexpected results suggest the need for further study on the subjective effects of hismanal.

Self Ratings

Self reports of sleepiness, using the Stanford Sleepiness Scale decreased throughout the day, with a suggested increase at 2:00 pm which remained at the 4:00 pm session. The increase in sleepiness during the afternoon corresponds to the decreased performance trends seen in Unstable Tracking, Code Substitution, Logical Reasoning, Pattern Comparison, Manikin, and Serial Addition/Subtraction, and to the physiological measurement of systolic blood pressure. These results may be indicative of circadian patterns and/or sleepiness following ingestion of lunch. The temporal decrease in sleepiness is inversely related to the mood subscales for vigor-activity. Reported levels of sleepiness were higher for the benadryl group than for both placebo and hismanal groups during the two morning sessions, while high levels of fatigue were reported through the 2:00 pm session for both Mood Scale II and the Profile of Mood States. These results serve to underscore findings on the two mood scales and substantiate prior research which identified sleepiness, drowsiness, and fatigue as occuring for one to five hours post

ingestion of benadryl (Carruthers et al., 1978; Cohen et al., 1987; Jaattela et al., 1971; Moskowitz and Burns, 1988). No differences were expected or identified for the hismanal group on sleepiness levels.

There was a difference in self rating of medication according to which drug/medication the subject received. Subjects responded that they had received a placebo more often when actually receiving a placebo. Subjects also responded as having received an antihistamine post benadryl, but did not respond as having received an antihistamine post hismanal. These results are expected as few side effects have been reported with hismanal ingestion (Vanden Bussche et al., 1984, as reported by Richards et al., 1984).

Subjects perceived their performance as poorer post ingestion of benadryl versus placebo and hismanal for three hours post ingestion. It appears that subjects were able to evaluate their own performance on more complex tasks as indicated by both errors and mean reaction time scores and were unable to correctly assess their performance on four-choice reaction time, time estimation, and interval production tasks. Although the correlations were low, these results tend to support research in which subjects were able to recognize their performance decay on a driving task (Betts et al., 1984) and on psycho-motor performance tasks (Moskowitz and Burns, 1988), but were unable to correct it.

The research results suggest the following conclusions:

(1) The Stanford Sleepiness Scale is sensitive to the drug effects of the antihistamines used in this study for three hours post ingestion. This rating scale is recommended for further use in antihistamine research.

(2) As stated above, further research is needed for elucidation of temporal effects.

(3) The correlations for actual versus perceived performance, while low, suggest the need for further research.

Summary of Subjective and Physiological Data

Clearly the mood scales used in this study were able to register both time of day and drug effects. Activity levels were lowest during the two morning sessions and increased throughout the course of the day. The Stanford Sleepiness Scale was inversely related to reported activity levels. Results of both the activity scales and the sleepiness scale reflect suggested temporal effects noted on performance tasks of lower performance during the afternoon sessions (2:00 pm and 4:00 pm).

A higher level of tension, greater fatigue, and a lower level of activity was experienced by the benadryl group. These results support findings in which symptoms of sleepiness, drowsiness, mental and physical sedation, fatigue, and lowered ability to concentrate post benadryl ingestion have been reported (Carruthers et al., 1978; Cohen, Hamilton, and Peck, 1987; Jaattela et al., 1988; Moskowitz and Burns, 1988) and refute the finding of no mood effect found by Miller et al. (1988).

The results of the two mood scales are in marked agreement on the activity and fatigue scales. Although the activity level reported for the hismanal group was higher than that of the benadryl group on the POMS, greater activity was noted for the placebo group than for both the hismanal and benadryl groups at one hour post ingestion of benadryl on both mood scales. At three hours post ingestion, both the placebo and the hismanal group reported higher levels of activity than the benadryl group. The benadryl group reported higher levels of fatigue than did either the placebo or hismanal groups at one hour and three hours post ingestion. Higher levels of fatigue continued to be reported for the benadryl group than for the placebo group at five and seven hours post ingestion. Self reports of sleepiness on the Stanford Sleepiness Scale substantiate the findings of low activity and high fatigue for the benadryl group at one and three hours post ingestion. The Profile of Mood States also includes a subscale for confusion. The benadryl group reported higher levels of confusion than did the placebo group at one hour post ingestion and higher than either the placebo or hismanal groups at three hours post ingestion. The hismanal group reported higher confusion than the placebo group at one hour post ingestion, but remained lower than the benadryl group. These results tend to extend the time that subjective changes are noted due to the disruptive effects of benadryl (Gengo et al., 1989) by one hour.

Subjects responded that they had received a placebo more often when actually receiving a placebo. Subjects also responded as having received an antihistamine post benadryl, but did not respond as having received an antihistamine post hismanal. Subjects perceived their performance as poorer post benadryl versus placebo and hismanal during the first two hours post ingestion. Perceived performance and actual performance were found to be significantly correlated on all tasks except the time based tasks of four-choice reaction time, time estimation, and interval production.

Hismanal versus Benadryl

Performance decrements were found on the Following Directions task at one hour post benadryl ingestion. At one and a half hours post benadryl ingestion, diminished performance was seen on the unstable tracking task and at three hours post, diminished performance was noted on the serial addition/subtraction task. All three findings were different than those comparing hismanal and placebo. These results extend the finding of performance effects lasting for two hours post benadryl ingestion on driving performance and digit symbol substitution tasks (Gengo et al., 1989). The research results also suggest that the type of skill affected by ingestion of benadryl may vary by time post ingestion.

No performance decrements were found post hismanal ingestion. At five hours post ingestion, the hismanal group performed faster on the Serial Addition/Subtraction task. Three hours post ingestion, root-mean-square error for the benadryl group was higher than for the hismanal group, but not different from placebo. Not only were there no performance decrements noted post hismanal ingestion, on two occasions the hismanal group performed better than did the placebo group. On the basis of this research, hismanal appears superior to benadryl when high level performance is required (Table 1).

Drug effects were found which indicated higher levels of tension-anxiety and fatigue-inertia and lower levels of vigor-activity post ingestion of benadryl. At one and three hours post ingestion of benadryl, vigor-activity was lower on both mood scales (compared with placebo). Confusion was greater at one and three hours post benadryl ingestion compared with both placebo and hismanal, and at three hours compared with hismanal. Fatigue was greater at one, three, five, and seven hours post ingestion of benadryl versus placebo and greater at one and three hours post ingestion compared with hismanal. Both at one and three hours post ingestion of benadryl, sleepiness was greater than for hismanal and placebo. At one hour post ingestion of hismanal, vigor-activity was lower than with a placebo for both mood scales. Although vigor-activity was lower for the hismanal group compared with placebo, vigor-activity was still higher when compared with benadryl on the POMS. At three hours post ingestion, vigor-activity post hismanal was no different from placebo and higher than post benadryl . Confusion was greater for the hismanal group at one hour post ingestion compared with placebo; however, confusion was still lower than that seen with benadryl. Hismanal ingestion did not increase fatigue. Thus, on two occasions hismanal was rated lower than placebo (at one hour post ingestion

on vigor-activity and on confusion-bewilderment) and on these occasions, hismanal remained superior to benadryl. On the basis of the single therapeutic doses administered in this research, hismanal ingestion is clearly preferable to benadryl ingestion for avoidance of subjective symptomatology (Tables 2 - 5).

There were no differences in physiological measures with either medication. Subjects were able to determine when they received a placebo and when they received benadryl; but were not able to identify hismanal receipt as an antihistamine. Subjects perceived their performance as lower post benadryl ingestion at one and three hours post ingestion as compared with both placebo and hismanal.

Hismanal offers distinct advantages over the use of benadryl. Performance was not disrupted post hismanal ingestion; in fact, performance exceeded that of the placebo group on two occasions. On the two occasions that a subjective rating was lower for hismanal versus placebo, the rating was still higher for hismanal compared with benadryl. Based on this research, it is concluded that the use of hismanal is superior to benadryl when a high level of performance is required and when an individual desires to avoid negative subjective side effects. Hismanal appears to have excellent potential as a nonsedating antihistamine.

Identification of a medication that does not cause central nervous system deficits would allow military (or civilian) physicians to prescribe medications which would permit individuals to perform unhampered by either the symptoms of the illness or the side effects of the drug. For example, according to Whitehurst (1980) pilots will often ignore symptoms in order to be able to continue flying. Whitehurst (1980) also cautions against self medicating with over-the-counter pharmaceuticals and offers the guideline of restricting a pilot from flying when taking antihistamines and for 24 hours post final dosage or until all side effects have ceased, preferring to choose the longer of the two. If the risk of being "grounded" were lessened via use of an antihistamine which would not restrict flying, pilots (and other professionals) may be more inclined to seek the medical assistance they need.

RECOMMENDATIONS

In addition to the research needs mentioned above, for greater generalization of results, research needs to include women and subjects drawn from a more diverse population than healthy, young, college males. Individual differences in suceptibility may

be of research interest. As tolerance to the central effects such as sedation may develop so that sedation is no longer troublesome (Nicholson, 1983, as reported by Brandon, 1985, and the therapeutic effects of hismanal require either a loading dose or several days for symptom alleviation, research over an extended period of time is necessary. Drug concentration levels from blood samples that are drawn throughout the day should be included in the analysis. This research should also include therapeutic trials, performance data, and subjective ratings.

The addition of a control group which does not receive antihistamines but instead receives a placebo on all treatment days would serve to guard against subjects responding as if they had received an antihistamine. For example, as subjects are aware that they are going to receive all possible drug conditions, they may respond to symptom questionnaires as if they had received an antihistamine based on this knowledge rather than on their true perceptions/symptoms. The inclusion of a placebo-only control group would also permit a straight-forward analysis of possible learning effects. Coupled with the afore mentioned control for meals, a truer indication of circadian patterns would be revealed.

Performance tests which are used should be sensitive to the effects of drugs and should be validated. For example, although the Following Directions task was shown to be sensitive to the effects of benadryl, this was the first occasion of its use in a performance assessment of antihistamines. The Route Planning task did not show performance effects following antihistamine use, but it is unclear if this was due to the task requirements or to the software difficulties in recording data. Although laboratory techniques may be sensitive to the impairment effect of sedative drugs, validation of a laboratory test system with functional performance using drugs of known sedative potential is essential. As sustained attention and dual performance tasks appear to be more sensitive to the effects of drugs (as well as differentially affected by drugs), these tasks should be used and compared with simulations and/or actual performance.

TABLE 1

Summary Table of Significant Performance Measures

Dependent Variable	Hours Post Ingestion	Grouping	Mean	Drug
Following Directions				
Percent total hits	1	A	90.9286	Placebo
		A	90.3750	Hismanal
		B	84.3221	Benadryl
Serial Addition/subtraction				
Mean reaction time	3	A	1.2427	Benadryl
		B	1.0541	Hismanal
		B	1.0266	Placebo
	5	A	1.08589	Placebo
		A	1.04637	Benadryl
		B	0.92150	Hismanal
Unstable Tracking				
RMS error	1	A	18.9586	Benadryl
		B	15.8310	Placebo
		B	13.9310	Hismanal
	3	A	18.4379	Benadryl
		AB	16.0	Placebo
		B	15.0138	Hismanal

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE 2

Summary Table of Significant Subjective Measures

Dependent Variable	Grouping	Mean	Drug
POMS			
Tension - anxiety	A	4.7796	Benadryl
	B	3.8799	Hismanal
	B	3.6938	Placebo
Vigor - activity	A	14.7345	Placebo
	A	14.4730	Hismanal
	B	13.0202	Benadryl
Fatigue - inertia	A	6.4909	Benadryl
	A	5.2609	Hismanal
	A	5.2244	Placebo

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE 3

Summary Table for Vigor-Activity scale on Mood Scale II and the POMS

Dependent Variable	Grouping	Mean	Drug
Vigor - activity			
8:00 am			
Mood Scale II	A	2.2176	Placebo
	B	2.0329	Hismanal
	B	1.8565	Benadryl
POMS	A	15.2500	Placebo
	B	4.8057	Hismanal
	C	1.8056	Benadryl
10:00 am			
Mood Scale II	A	2.0876	Placebo
	A	2.0824	Hismanal
	B	1.8570	Benadryl
POMS	A	14.8929	Placebo
	A	14.5186	Hismanal
	B	11.5926	Benadryl

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE 4

Summary Table for Fatigue-Inertia scale on Mood Scale II and the POMS

Dependent Variable	Grouping	Mean	Drug
8:00 am			
Mood Scale II	A	1.7590	Benadryl
	B	1.5319	Hismanal
	B	1.3814	Placebo
POMS	A	8.8519	Benadryl
	B	5.8146	Hismanal
	B	4.2857	Placebo
10:00 am			
Mood Scale II	A	1.7665	Benadryl
	B	1.5081	Placebo
	B	1.3810	Hismanal
POMS	A	9.0741	Benadryl
	B	5.9286	Placebo
	B	4.6296	Hismanal
12:00 pm			
Mood Scale II	A	1.5170	Benadryl
	A B	1.4519	Hismanal
	B	1.2933	Placebo
POMS	A	6.0370	Benadryl
	A B	5.3214	Hismanal
	B	3.8214	Placebo
2:00 pm			
Mood Scale II	A	1.6267	Benadryl
	A B	1.5086	Hismanal
	B	1.4048	Placebo
POMS	A	7.0000	Benadryl
	A B	5.2857	Hismanal
	B	4.9286	Placebo

Note: Means with the same letters are not significantly different, $p > 0.05$.

TABLE 5

Summary Table for Confusion, Sleepiness, and Performance Scales

Dependent Variable	Grouping	Mean	Drug
Confusion - Bewilderment			
8:00 am	A	5.6667	Benadryl
	B	4.6668	Hismanal
	C	3.3571	Placebo
10:00 am	A	5.7778	Benadryl
	B	3.9629	Hismanal
	B	3.6429	Placebo
Sleepiness			
8:00 am	A	4.0741	Benadryl
	B	3.1071	Hismanal
	B	2.8571	Placebo
10:00 am	A	3.8889	Benadryl
	B	3.0000	Hismanal
	B	2.8929	Placebo
Performance			
8:00 am	B	3.8214	Placebo
	B	3.7857	Hismanal
	A	3.0000	Benadryl
10:00 am	B	3.7143	Placebo
	B	3.5714	Hismanal
	A	3.0741	Benadryl

Note: Means with the same letters are not significantly different, $p > 0.05$.

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